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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,888	09/29/2003	Ellen W. Evans	oc01600	1648

24265 7590 09/20/2006

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,888	EVANS ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/04/04; 2/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application claims priority under 35 U.S.C § 119(e) from the provisional application 60/414,948 filed on 9/30/2002.

Claim Objections

Applicant is advised that should claim 1 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of familial benign hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, renal secondary hyperparathyroidism, osteoporosis, malignancy-associated

hypercalcemia (MAH) and humoral hypercalcemia of malignancy (HHM), with one of the specific compounds listed in claim 2 and for the combination of said compounds with one of the compounds listed in claim 10, does not reasonably provide enablement for the treatment of all diseases and disorders associated with calcium homeostasis or the **prevention** of hypercalcemia and other diseases associated with calcium homeostasis or for the use of a combination of a compound of formula I with **any** compound used for the treatment of a disorder associated with calcium homeostasis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to the method for the treatment of disorders associated with calcium homeostasis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The claimed invention is a therapeutic method for preventing or treating a disorder of calcium homeostasis.

The state of the prior art:

Calcium homeostasis is involved in a multitude of essential cellular functions. (Carmeliet G. et. al., Best Practice & Research Clinical Endocrinology & Metabolism; 2003, 529-546; Abstract Page 529, and Figure 1 Page 530). Calcium homeostasis depends on integrated regulation of calcium fluxes with respect to the intestine, kidneys and bone. (Carmeliet, G., Page 529, Abstract). Calcium homeostasis is controlled by calcium itself calcium receptor and several hormones, including parathyroid hormone. (Carmeliet, G., Page 529, Abstract). Calcium homeostasis is disturbed by mutations to the calcium sensing receptor, inappropriately high or low levels of parathyroid hormone, resistance to parathyroid hormone effects. (Carmeliet, G., Page 529, Abstract). It is highly unlikely that several types of disorders caused by multiple pathways can be treated by a single compound and even more unlikely that said disorders can be prevented by said compounds, especially in case of disorders caused by genetic mutations.

Farnesylation inhibitor B-1086 has been used to treat malignancy associated hypercalcemia. (Specification, Page 3, lines 8-15). B-1086, a well known inhibitor or farnesyl transferase was found to induce a near normalization

of malignancy associated hypercalcemia and elevated parathyroid related peptide levels in serum. (Eskens, Cancer Treatment Reveiws; 2000, 319-332; PTO-892, Cited by the examiner). Tricyclic compounds of Formula A of the instant application are well known for their activity against farnesyl transferase. (Doll et. al, WO/97/23478; Page 15, lines 1-15 and; PTO-1449, Included by the applicant). Compound SCH 66336 is well known for its activity as an inhibitor of farnesyl transferase. (Eskens, Page 327, Figure 6 and Table2).

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The predictability or lack thereof in the art:

Prevention of disorders associate with calcium homeostasis is not the same as the treatment of said diseases or disorders. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The breadth of the claims:

The current claims are deemed very broad since they include the treatment and prevention of any disease associated with calcium homeostasis. Calcium homeostasis involves a large number of disorders including several hereditary disorders. (Carmeliet, G., Page 529, Abstract, and Page 531 Paragraph 3).

The amount of direction or guidance presented:

The specification does not provide any clear guidance to use the claimed method for the prevention of any disorders associated with calcium homeostasis. The specification reports studies of nephrotoxicity (Table 1-4, Page 23-24) of the compound of Formula I, (SCH 66336) in rats, as well as the effect of said compound on calcium secretion in urine. (Tables 4-7). The specification states that the date from the study using the compound of Formula I strongly suggests that other compounds of similar structure will also be useful. However, no reason for the expectation was given.

There are no methods or examples of using any compound other than the compound of Formula I is given. There are no examples or methods for the use of any compounds in combination with any compounds is given.

The presence or absence of working examples:

The examples 1-2 relates to the study of toxicity of the compound of Formula I. Note that the compound of Formula I is a well-known pharmaceutical in clinical use. Example 2 involves the microscopic evaluation of rats that were given the compound of formula I, which shows that the parathyroid glands are affected by the administration of said compound. However, the examples do not indicate that the rats were suffering from any particular disorders associated with calcium homeostasis.

There are no examples of the use of any other compound or any compound in combination with the compounds of Formula A for the treatment of any particular diseases associated with calcium homeostasis.

The quantity of experimentation necessary:

The usefulness of one compound to have an effect on the calcium homeostasis, does not mean that compound and all similar compounds are useful for the treatment of any disease or disorder associated with calcium homeostasis. Furthermore, there is no guarantee that such compound, similar compounds or a combination of compounds will be useful in the prevention of any diseases associated with calcium homeostasis. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy.

In particular, one skilled in the art would need to know whether the regular administration of the combination in the claimed form over the long term would adversely affect the health of the subject. Additionally, one skilled in the art, in order to practice the invention for prevention of disease would need to know whether the preventive effect remains potent over the long term. Unless the therapy absolutely eliminates all of the diseases associated with calcium homeostasis over the long term, the drug cannot be considered a preventive therapy.

In order to answer these questions, in the absence of any existing data, one skilled in the art, in order to practice the invention, would have to undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or sheeps. Accomplishing such a task for the myriad of symptoms that can be considered associated with calcium homeostasis would require an undue amount of experimentation for the practice of full range of the claimed invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of diseases claimed herein absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3, 17 and 18, the only independent claims in the application recites the phrase "disorder of calcium

homeostasis". The specification provides an example of a disorder of calcium homeostasis as "hypercalcemia." (Specification, Page 5, lines 5-10). However, the term is not clearly defined so that one of ordinary skill in the art would be apprised of the metes and bounds of claimed invention. Note that exemplification is not a clear definition. As such, said recitation renders the claims indefinite.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of the phrase "disorder of calcium homeostasis" renders the claim indefinite. As such, one of ordinary skill in the art would not be apprised of the metes and bounds of claimed invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the limitation "the medical condition" in the first line of claim 4. There is insufficient antecedent basis for this limitation in the claim. Claim 1, from which 4 depends, merely recites "a disorder of calcium homeostasis".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (PTO-1449; Included by the applicant) in view of Eskens et.al. (PTO-892, Cited by the examiner) further in view of applicant's admission regarding the relation between farnesyl transferase inhibitors and disorders of calcium homeostasis. (Specification, Page 3, lines 8-15).

Doll et. al. discloses a series of compounds for the inhibition of Farnesyl transferase. (Page 1, lines 10-15, and Page 2 to 13). Tricyclic compounds of Formula A of the instant application are disclosed for their activity against farnesyl transferase. (Doll et. al, WO/97/23478; Page 15, lines 1-15 and; Page 2 line 10 to Page 13, line10). Doll et. al. further discloses the use of said compounds in patients and with pharmaceutically acceptable carriers. (Page 115, line 5 to Page 116 line 5). Doll et. al further discloses the use of compounds of Formula A for the treatment of a variety of cancers, including thyroid follicular cancer. (Page 116, lines 4-10).

Doll et. al. does not explicitly disclose the use of compounds of Formula A for the treatment of disorders of calcium homeostasis.

Eskens et. al. discloses that Ras oncogenes and Ras oncoproteins are found with high frequency in various human tumour types and that enzyme farnesyl transferase is involved in the activity of Ras. (Page 319, First Paragraph). One of the diseases associated with Ras tumours is malignancy associated hypercalcemia. (Eskens, Page 324, Column 1, Paragraph 4) B-1086, a well known inhibitor or farnesyl transferase was found to induce a near normalization of malignancy associated hypercalcemia and elevated parathyroid related peptide levels in serum. (Eskens, Page 324, Column 1, Paragraph 4). Compound SCH 66336 is well known for its activity as an inhibitor of farnesyl transferase. (Eskens, Page 327, Figure 6 and Table2).

Applicant admits that 10-20% of cancer patients suffer from parathyroidism. (Specification, Background of the invention, Page 2, 17-25). Applicant further admits of the relation between Farnesyl protein and disorders associated with calcium homeostasis. (Specification, Page 3, lines 8-15). Farnesylation inhibitor B-1086 has been used to treat malignancy associated hypercalcemia. (Specification, Page 3, lines 8-15).

It would have been obvious to one of ordinary skill in the art to use compounds of Formula A and in particular the compound of Formula I for the treatment of disorders associated with calcium homeostasis. Furthermore, it would have been obvious to one of ordinary skill in the to use the specific

compounds of Claim 18 because they are structurally similar to compounds of Formula A, well known for their activity against Farnesyl transferase.

One having ordinary skill in the art would have been motivated to do this because compounds of Formula A are well known for their inhibitory activity against Farnesyl transferase and Farnesyl transferase is well known for its involvement in disorders of calcium homeostasis. Furthermore, one of ordinary skill in the art would have been motivated the specific compounds of Claim 18 because they are structurally similar to compounds of Formula A, well known for their activity against Farnesyl transferase.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (PTO-1449; Included by the applicant) in view of Eskens et.al. (PTO-892, Cited by the examiner) further in view of applicant's admission regarding the relation between farnesyl transferase inhibitors and disorders of calcium homeostasis. (Specification, Page 3, lines 8-15), further in view of Nemeth et. al. (PTO-892, Cited by the examiner).

The disclosure of Doll et. al. is discussed above.

Doll et. al. does not explicitly disclose a combination of a compound Formula A with a second compound used for treating a disorder of calcium homeostasis.

Nemeth et. al. discloses the use of compounds NPS R-568, and NPS R-467 as useful for the treatment of calcium homeostasis related disorders. (Page 4040, Abstract).

The disclosure of Eskens et. al. and the admissions in the specification are discussed above.

It would have been obvious to one of ordinary skill in the art to use compounds of Formula A and in particular the compound of Formula I in combination with another compound used for the treatment of disorders associated with calcium homeostasis.

One having ordinary skill in the art would have been motivated to do this because compounds of Formula A are well known for their inhibitory activity against Farnesyl transferase and Farnesyl transferase is well known for its involvement in disorders of calcium homeostasis, and NPS R-568 and NPS R-467 are well known for the treatment of disorders associated with calcium homeostasis.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9/17/06

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